Prescriptions for contraindicated category X drugs in pregnancy among women enrolled in TennCare

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Summary

Filling of prescriptions for medications labelled as category X by the United States Food and Drug Administration (considered to be contraindicated for use in pregnancy) was identified among 95 284 women enrolled in TennCare, Tennessee's programme for Medicaid enrollees and individuals without health insurance. Using administrative claims data, 391 women (4.10/1000) were identified as having filled category X prescriptions during pregnancy. This included 118 women (1.24/1000) who filled prescriptions for non-contraceptive oestrogens, 81 (0.85/1000) for sedatives, and 71 (0.75/1000) for statins. While many women had physician visits with a diagnosis consistent with a possible indication for an individual drug outside of pregnancy, none of these indications is included for use during pregnancy. Older women and disabled women were more likely than younger women ($P < 0.0001$) and women enrolled for other reasons ($P < 0.0001$) to fill category X prescriptions. Nearly two-thirds of the 391 women filled prescriptions after clinical signs or pregnancy tests would indicate pregnancy; nearly 40% filled a category X prescription after a pregnancy-related physician visit. Although the absolute rate of category X medication use in pregnancy is low, substantial numbers of women and their fetuses are exposed during pregnancy. Women above the age of 35 years and women enrolled in TennCare because of disabilities were more likely to fill prescriptions for category X medications during pregnancy than others, implying that risk communication to practitioners and women should focus on identification of these women to reduce their risk of exposure.

Introduction

The United States Food and Drug Administration categorises prescription medications for use in pregnancy according to fetal risk. Category X is reserved for those few agents where risk clearly outweighs benefit.[1] Category X medications are so designated if 'studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both.'[1] For these medications, either an alternative medication is available for treatment of a condition or the treatment may safely be delayed until completion of the pregnancy.[1] While it is recognised that the FDA categorisation has weaknesses, including concerns about its ability to inform about actual risk,[2] it is currently recommended that pregnant women or women who may become pregnant should not use these drugs. Little is known about the use of category X medications in any United States population. With recent increase in use of many medications,[3] it is important to identify whether or not potentially dangerous medication exposures are occurring, especially in vulnerable populations. If certain groups of women are exposed unnecessarily to these medications, then risk communication and monitoring procedures could be focused in specific areas. This study was designed to identify filled prescriptions for category X drugs among pregnant women enrolled in TennCare, Tennessee's managed care programme for Medicaid-eligible enrollees and individuals lacking health insurance.

Methods

The study population and outcomes of interest were identified from Tennessee birth certificate and Medicaid (TennCare) files. These files have been validated

and have served as an unbiased source of population and prescription drug information in several studies.[4–8] Women were identified from Tennessee birth certificate files and were included in this retrospective cohort study if they delivered a baby between 1 January 1995 and 31 December 1999 with enrolment in TennCare from 30 days before pregnancy until delivery. We identified the mother's age, race, county of residence, and category of TennCare enrolment from the enrolment files. Race was included because of evidence from prior studies documenting differences in filling of medications among racial and ethnic groups and was identified from birth certificate files.[9]

Prescriptions for category X drugs between 30 days before the date of the last menstrual period (LMP) and the date of delivery were identified from TennCare pharmacy files. All category X drugs available during the study period were identified from the medical literature[1,10–19] and included: non-contraceptive oestrogens (oestradiol, conjugated oestrogen with methyltestosterone or testosterone), statins (lovastatin, atorvastatin, pravastatin, simvastatin, fluvastatin, cirivastatin), warfarin derivatives (warfarin, bishydroxycoumarin, anisindione), quinine, benzodiazepine sedatives (flurazepam, quazepam, temazepam, triazolam), non-oestrogen hormones (leuprolide, danazol, clomiphene), vitamin A preparations (etretinate, isotretinoin, menadione, and vitamin A), ribavirin, chenodiol, live vaccines (measles, mumps, rubella), iodinated glycerol, aminopterin, and misoprostol. Because classification of an individual drug's pregnancy risk may change over time, we reviewed the Physicians' Desk Reference for each of the study years[10–14] and both the 4th and 5th editions of a monograph describing drugs in pregnancy.[1,15] We included only drugs that were labelled as category X medications for all years of the study period.

We recorded the LMP and the day of delivery from the birth certificate file. This methodology has been validated previously by our research group using maternal and newborn hospital records.[4] In the validation study, we found concordance between the birth certificate LMP and the hospital records in 84.2% of the records reviewed, with concordance of date of birth and hospital records in 99% of the records reviewed.[4] When the LMP date was missing or implausible (10.7% of all birth certificates), estimates were made of LMP from birthweight, using the race and calendar-year specific distributions of gestational age in the population for whom both gestational age and birthweight were known. When LMP day of the month was missing, we imputed a value of 15.[4] A woman was considered to have been exposed to a drug in a given trimester (Trimester 1: LMP to day 90 of gestation; 2: from day 91 to day 180; and 3: from day 181 to the date of birth) if she filled one or more prescriptions for it during the trimester or the days' supply from a prescription filled in the previous trimester overlapped into the next trimester.

Clinical profiles were developed for each woman who filled a prescription for a category X drug during pregnancy. Profiles included all health care encounters occurring 30 days before the LMP up to the date of delivery. Diagnoses were then manually reviewed for each woman to identify a possible indication for use of the drug, using Physicians' Desk Reference indications,[10–14] or indications included in the medical literature.[18] We have linked health care encounters to prescription claims before, linking 78–86% of prescriptions to a claim with a possible diagnosis.[5–7] For women with multiple visits temporally linked to a prescription, the primary diagnosis from the visit closest to the fill date was used. If no possible indication was found among the primary diagnosis fields for a woman's encounters, secondary diagnoses were searched in a similar fashion. For drugs and indications related to chronic health conditions which are likely to be present throughout pregnancy (e.g. warfarin used for women with artificial heart valves), visits occurring at any time during pregnancy were searched for a possible indication. For drugs and indications related to more acute problems (e.g. benzodiazepines for back strain), possible indications were required to occur during the period from 30 days before the fill date up to the fill date.

Comparisons were made among women who filled category X prescriptions and women who did not, using χ^2 analysis (SAS statistical software 8.2; SAS Institute, Cary, NC). The study was reviewed and approved by the Vanderbilt University Institutional Review Board, the State of Tennessee Institutional Review Board, the Tennessee Department of Health, and the TennCare Bureau.

Results

There were 404 359 births in Tennessee between 1995 and 1999; 223 947 were enrolled in TennCare at the time of delivery (55.4%). Of these women, 95 284 (42.5%) were continuously enrolled during pregnancy.

The average age of women in the cohort was 23.1 ± 5.4 years; 67.7% were <25 years of age at delivery; 4.3% were >35 years of age. Forty-two per cent of the mothers were black. Women qualified for TennCare through the Aid to Families with Dependent Children programme (65.6%), being uninsured/uninsurable (27.2%), or having a disability (7.2%).

Among these 95 284 women, prescriptions for category X drugs were filled by 391 (4.10/1000 women) (Table 1). Non-contraceptive oestrogens, sedatives, and statins together accounted for 69% of category X drug use. Non-oestrogen hormones, warfarin derivatives, quinine preparations, misoprostol, isotretinoin, vitamin A preparations, and iodinated glycerol accounted for the remainder of prescriptions filled. There were no prescriptions filled for ribavirin, chenodiol, or live vaccines.

Among the 391 women filling prescriptions for category X medications, 317 (81.1%) had a physician visit linked to the prescription. For 173 women (54.6% of those with a visit), the diagnosis for the visit was consistent with a possible indication. For the other 144 women (45.4% of those with a visit), the most common diagnosis was for routine pregnancy care.

For the 45 women filling prescriptions for non-contraceptive oestrogens with a possible indication, the most commonly identified diagnoses included menstrual irregularities and infertility (20 women, 44.4%). Other possible indications included other gynaecological problems (13 women, 28.9%) and threatened labour (10, 22.2%) (this was formerly considered by some providers to be a clinical indication for oestrogen but is not currently an indication for oestrogen). Among the 27 women filling prescriptions for non-oestrogen hormones with a possible indication 21 (77.7%) had visits for menstrual irregularities or infertility; 4 (14.8%) had visits for endometriosis or other gynaecological problem; 2 (7.4%) had visits for endocrine insufficiencies.

For women filling prescriptions for sedatives with a possible indication ($n = 43$), 24 (55.8%) had diagnoses related to anxiety or psychiatric disorders; 7 (16.3%) had a visit for back pain. An additional 7 women (16.3%) filled sedative prescriptions within 1 day of a hospital admission for threatened labour early in pregnancy. Five women (11.6%) had a diagnosis of insomnia temporally related to the prescription fill date. No women filling a prescription for sedatives had visits for alcohol or drug withdrawal.

Among 38 women filling prescriptions for statin medications with a possible indication, 18 (47.4%) had diagnoses of hypercholesterolaemia or dyslipidaemias, while another 20 (52.6%) had diagnoses of underlying conditions that might predispose a woman to dyslipidaemias (cardiac disease, diabetes, endocrine disorders, and hypertension). Among the 28 warfarin derivative users with a possible indication, 17 (60.7%) had diagnoses of coagulopathies or thrombosis, while 8 (28.6%) had diagnoses of cardiac valve disease or cardiac disease, and 3 (10.7%) had a diagnosis of sys-

Table 1. Use of Category X drugs by trimester among pregnant women enrolled in TennCare, Tennessee's managed care programme for Medicaid enrollees and individuals without health insurance, 1995–99

	First trimester		Second trimester		Third trimester		Any use during pregnancy[a]	
Medication	*n*	Rate[b]	*n*	Rate[b]	*n*	Rate[b]	*n*	Rate[b]
Non-contraceptive oestrogens	74	0.78	48	0.50	40	0.42	118	1.24
Benzodiazepine sedatives	31	0.33	16	0.17	45	0.47	81	0.85
Statins	59	0.62	18	0.19	12	0.13	71	0.75
Non-oestrogen hormones	45	0.47	2	0.02	1	0.01	46	0.48
Warfarin derivatives	41	0.43	16	0.17	8	0.08	44	0.46
Quinine	21	0.22	8	0.08	7	0.07	30	0.31
Misoprostol	3	0.03	1	0.01	3	0.03	6	0.06
Isotretinoin	1	0.01	1	0.01	1	0.01	3	0.03
Vitamin A preparations	0	0.00	1	0.01	1	0.01	2	0.02
Iodinated glycerol	3	0.03	1	0.01	0	0.00	4	0.04
Any category X use	268	2.81	111	1.16	113	1.19	391	4.10

[a]Because some women filled prescriptions during multiple trimesters, row totals may not add up.
[b]Rate per 1000 births, among the 95 284 births to TennCare mothers during the study period.

Table 2. Relationship of category X prescription to day of gestation and pregnancy diagnosis among women covered by TennCare who filled prescriptions for category X medications

		Prescription occurring later than 28 days after the last menstrual period				Prescriptions occurring after the diagnosis of pregnancy			
		1st prescription		Any prescription		1st prescription		Any prescription	
	n filling any prescriptions	*n*	%[a]	*n*	%[a]	*n*	%[a]	*n*	%[a]
Any category X	391	177	45.3	239	61.1	129	33.0	151	38.6
Non-contraceptive oestrogens	118	65	55.1	86	72.9	42	35.6	50	42.4
Benzodiazepine sedatives	81	60	74.1	65	80.3	52	64.2	55	67.9
Statins	71	26	36.6	38	53.5	18	25.4	23	32.4
Non-oestrogen hormones	46	4	8.7	6	13.0	4	8.7	5	10.9
Warfarin derivatives	44	5	11.4	24	54.6	3	6.8	8	18.2
Quinine	30	13	43.3	17	56.7	6	20.0	7	23.3
Misoprostol	6	4	66.7	4	66.7	3	50.0	3	50.0
Isotretinoin	3	2	66.7	2	66.7	2	66.7	2	66.7
Vitamin A preparations	2	2	100.0	2	100.0	2	100.0	2	100.0
Iodinated glycerol	4	3	75.0	3	75.0	2	50.0	2	50.0

[a]Expressed as percentage of women filling prescriptions for this medication.

temic lupus erythematosus (presumably at risk for coagulopathies). Among women filling quinine prescriptions during pregnancy, 12 (85.7%) had visits for muscle cramps or backache. One quinine user had a diagnosis of fever, but none had a diagnosis of malaria.

Filling of category X prescriptions in women older than 35 (12.1/1000) was nearly 10 times higher than women younger than 18 (1.5/1000) ($P < 0.0001$). Women in the older age group most commonly filled prescriptions for statins (37.5% of women in the older age group who filled category X prescriptions filled prescriptions for statins) and non-contraceptive oestrogens (31.3%). Prescription filling was similar among urban and rural residents, and remained relatively stable (4.3/1000 in 1995, 4.6/1000 in 1999) during the 5 study years. Women enrolled in TennCare because of disability were nearly three times more likely to fill prescriptions for category X medications during pregnancy than women enrolled through other categories ($P < 0.0001$). Women enrolled in TennCare because of disabilities most commonly filled prescriptions for benzodiazepines (31.8%), statins (19.7%), and warfarin derivatives (19.7%).

Among the 391 women filling prescriptions for category X drugs, 239 (61.1%) filled a prescription > 28 days following the last menstrual period, when clinical signs or pregnancy tests could indicate pregnancy (Table 2). Filling after the first 28 days of pregnancy occurred most commonly for non-contraceptive oestrogens, sedatives, vitamin A preparations, and iodinated glycerol. One hundred and fifty-one women (38.6%) filled a prescription for a category X drug even after a physician visit in which pregnancy was diagnosed. Filling after a diagnosis of pregnancy occurred most commonly for sedatives, isotretinoin, and vitamin A preparations.

Discussion

The TennCare population included 391 women (4.10/1000) who filled prescriptions for medications contraindicated during pregnancy. These findings differ somewhat from previous studies of category X medication use during pregnancy. In 1994, Rosa[19] identified 11 statin prescriptions among 229 101 Michigan Medicaid women who delivered babies between 1985 and 1992 (0.05/1000). The rate of statin use in pregnant women in the current study was more than 10 times that described by Rosa,[19] possibly reflecting the dramatic increase in use of statins in recent years.[3] In a more recent study describing use of medications among women delivering infants during 1996 in Haute-Garonne, south-west France, Lacroix *et al*.[20] identified the use of any Food and Drug Administra-

tion category X drug in 16/1000 women. The overall use of category X drugs in the current study was less than that described by Lacroix *et al.*,[20] perhaps related to the younger age of women enrolled in TennCare. The mean age of women in the Lacroix study was 29.8 years, compared with a mean age of 23.1 years in the current study.

While 81.1% of the women had a physician visit linked to the prescription date, many of these encounters were coded as pregnancy-related care, possibly reflecting the coding practices under circumstances where obstetric care is provided as a package. This suggests that a woman saw a physician for pregnancy-related care and filled a prescription for a contraindicated medication on the same day or soon after. It is possible that physicians providing care for which reimbursement is not tied directly to a visit may be less motivated to code specific diagnoses for an individual visit. There may even be circumstances where a woman was issued a prescription for a category X prescription by one physician before she was pregnant and then refilled the prescription during her pregnancy, without the knowledge of her pregnancy care provider. However, the *Guidelines for Perinatal Care* produced by the American College of Obstetricians and Gynecologists and American Academy of Pediatrics specifically state that physicians should record medications taken by pregnant women throughout pregnancy.[21] Thus, it should be possible for physicians to identify women taking category X medications, to avoid prescribing them for women who are or might possibly be pregnant, and to counsel women against taking these medications during pregnancy. While many of the women filling category X prescriptions during pregnancy had conditions which are appropriately treated with the medications in the current study, it is the Food and Drug Administration's recommendation that during pregnancy their risk outweighs potential benefits, even for these women.

Certain subgroups of women in the current study had substantially increased risk of filling prescriptions for category X drugs during pregnancy – those above the age of 35 and those enrolled in TennCare because of disability. Among these women, it is important for practitioners to consider carefully the likelihood of pregnancy before initiation of contraindicated medications. In many cases, prescriptions for category X drugs were filled well into pregnancy, presumably after clinical signs (missed menstrual period) or laboratory examinations (pregnancy tests) would indicate pregnancy.

Limitations of the data used in the current study could cause misclassification of exposure. Medicaid pharmacy files only contain claims for outpatient prescriptions.[5–8] Therefore, the study was not able to detect inpatient dispensing of category X drugs. Furthermore, the prescription files only indicate that a prescription was filled and cannot detect whether or not the pregnant woman took the medication as prescribed. It is possible that many stopped taking medications once pregnancy was diagnosed. However, in several instances, prescription filling occurred well after a physician encounter for pregnancy. Women terminating pregnancies (possibly because of knowledge of teratogenic effects of a medication) or women with spontaneous abortions would not be included in the cohort, causing underestimates of exposure to category X medications.

An additional limitation is the inability to identify pregnancy outcomes. Because the outcomes of prenatal exposure to the drugs included in this study are both disparate and extremely rare, sample size was not sufficient to determine whether or not there were fetal malformations among exposed infants for specific drugs. Finally, because the study includes women enrolled in TennCare, the results may not be generalisable to other populations. The TennCare population includes disproportionate numbers of mothers < 25 years of age, teenage mothers, mothers with <12 years education, and African-American mothers.[7,8] Another limitation is the fact that only 61% of the mothers filled prescriptions after 28 days of pregnancy. However, this still represents 239 women who filled prescriptions and thus would possibly benefit from counselling about pregnancy avoidance while taking these medications.

It should also be noted that the current system used by the FDA to label pregnancy risk has its limitations.[2] The FDA labelling system was intended to provide guidance to prescribers and not to estimate differential teratogenic risk. Thus, many of the assignments to risk categories are based on limited data because of a lack of studies of specific drug exposures. In addition, drugs within a given category may have very dissimilar reproductive risks. For example, the risks for warfarin derivatives are well described and specific whereas the risks for statins are more theoretical.[1,2] Confusion among labels of related drugs (e.g. benzodiazepines) may confuse providers prescribing indi-

vidual medications.[1,10–15] It is also recognised that many of the drugs included in this study have indications for conditions of major clinical import. For example, warfarin derivatives play an important role in the care of women with prosthetic heart valves and statins play an important role in women with dyslipidaemias. However, in all of these instances, there is either an alternative medication (heparin in place of warfarin)[1] or the sequelae of the condition are of such a long-term nature that no current evidence supports the use of the drug during the relatively brief period of pregnancy (e.g. statins).

The findings of this study emphasise the need for careful monitoring of care delivery to women of childbearing potential. Despite the limitations of the pregnancy risk categorisation system, the Food and Drug Administration recommends that no women should be exposed to category X drugs during pregnancy.[1,10–14,18,22] Risk communication to practitioners could be focused on practitioners delivering care to women at greatest risk for exposure to category X drugs: women over the age of 35 and women with chronic health conditions. Risk communication could also focus on these groups of women to educate them to avoid pregnancy or to stop use of these medications if pregnancy is suspected. Finally, monitoring systems at the pharmacy level could allow for avoidance of dangerous exposures and provide further opportunities for feedback to practitioners and patients.

Acknowledgements

Dr Cooper received support from the Generalist Physician Faculty Scholars Program of the Robert Wood Johnson Foundation (#03816). Dr Ray received support from the Centers for Education and Research in Therapeutics (CERT) program of the Agency for Health Care Research and Quality (#1U18HS10384-01) and from the Food and Drug Administration (cooperative agreement #FDU-001646).

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